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Distinct functional connectivity of limbic network in the washing type obsessive–compulsive disorder

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ABSTRACT

Neurobiological models of obsessive–compulsive disorder (OCD) emphasize disturbances of the corticostriatal circuit, but it remains unclear as to how these complex network dysfunctions correspond to heterogeneous OCD phenotypes. We aimed to investigate corticostriatal functional connectivity alterations distinct to OCD characterized predominantly by contamination/washing symptoms.

Functional connectivity strengths of the striatal seed regions with remaining brain regions during the resting condition and the contamination symptom provocation condition were compared among 13 OCD patients with predominant contamination/washing symptoms (CON), 13 OCD patients without these symptoms (NCON), and 18 healthy controls. The CON group showed distinctively altered functional connectivity between the ventral striatum and the insula during both the resting and symptom-provoking conditions. Also, the connectivity strength between the ventral striatum and the insula significantly correlated with contamination/washing symptom severity. As common connectivity alterations of the whole OCD subjects, corticostriatal circuits involving the orbitofrontal and temporal cortices were again confirmed.

To our knowledge, this is the first study that examined specific abnormalities in functional connectivity of contamination/washing symptom dimension OCD. The findings suggest limbic network dysfunctions to play a pivotal role in contamination/washing symptoms, possibly associated with emotionally salient error awareness. Our study sample allowed us to evaluate the corticostriatal network dysfunction underlying the contamination/washing symptom dimension, which leaves other major symptom dimensions to be explored in the future.

1. Introduction

Neuroimaging studies have made critical advances in elucidating the neural mechanisms that underlie obsessive–compulsive disorder (OCD). Reports of functional neuroimaging have emphasized the cortico–striato–thalamo–cortical (CSTC) circuit as central to the neurobiological model of OCD (Saxena, 2003). The development of alternative mapping techniques to examine brain connectivity features has made it possible to more directly demonstrate relationships between specific brain regions (Fox and Raichle, 2007). In OCD, resting-state connectivity analyses lent support to the prevailing hypothesis that abnormalities of the CSTC circuit are apparent in a large-scale brain network level (Harrison et al., 2009; Sakai et al., 2011). However, more recent studies suggest the existence of broader abnormalities that involve the temporo-parietal cortex and limbic regions in the OCD circuit (Del Casale et al., 2011).

With regards to the heterogeneity of OCD, various phenotypes may contribute to the discrepant neuroimaging results. Factor analytic studies have identified stable symptom dimensions that are related to different treatment responses (Mataix-Cols et al., 1999), comorbidities,(Mataix-Cols et al., 2000), and genetic transmission (Alsobrook et al., 1999), as well as distinct neural systems (van den Heuvel et al., 2009). Thus, there may be distinct functional abnormalities of the corticostriatal network that correspond to different OCD phenotypes. When exploring this hypothesis, symptom provocation protocols have the advantage of eliciting neural patterns more relevant to symptom emergence (Rotge

Abbreviations: OCD, obsessive–compulsive disorder; CON, contamination/washing symptoms; NCON, non-CON.

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et al., 2008). Investigation of functional networks using a symptom provocation paradigm targeted to elicit a certain OC symptom dimension may provide important information relevant to identifying specific abnormalities in OCD circuits. However, there is a paucity of studies that have examined distinct pattern of OCD circuit by symptom dimension.

The contamination/washing symptom dimension is one of the most common symptom dimensions in individuals with OCD (Rasmussen and Eisen, 1992). Patients with predominantly contamination/washing symptoms are characterized by strong avoidance and elevated disgust sensitivity, suggesting that this dimension of OCD may be closer to a "limbic spectrum disorder" (Mataix-Cols and van den Heuvel, 2006). Previous studies on the contamination/washing dimension of OCD using a symptom provocation paradigm reported greater activations in limbic areas, such as the insula and the parahippocampal gyrus, as well as the ventral part of the prefrontal cortex during symptom provocation (Mataix-Cols et al., 2003, 2004; Phillips et al., 2000; Shapira et al., 2003). Although these findings are still inconclusive, they suggest that distinct neural systems mediate different symptom dimensions, in contrast to the common neurobiological changes found in OCD patients as a whole, such as alterations of the orbitofrontal cortex (Pujol et al., 2004; van den Heuvel et al., 2009) and ventral striatum (Pujol et al., 2004). Direct evidence is still scarce at a network level in regards to the heterogeneity of the disorder. Based on prior knowledge of the CSTC circuit and symptom provocation studies, we hypothesized that the limbic circuit may be involved in the pathophysiology of the contamination/washing dimension of OCD.

In the present study, we aimed to explore functional connectivity alterations specific to the contamination/washing dimension of OCD. For comparison, we included both OCD patients without contamination/washing symptoms and healthy controls (HC). An augmented reality paradigm (Ku et al., 2008) that simulates visual illusory stimuli in an ecologically valid manner to provide subjects with the experience of virtual stimuli mixed with a real image was used to effectively provoke contamination symptoms in MRI device. We hypothesized that OCD patients with predominant contamination fears and washing rituals would demonstrate distinct functional connectivity patterns while processing the symptom-provoking stimuli compared to patients without these symptoms and healthy controls. We expected that the identified functional connectivity abnormalities in the contamination-based OCD would be associated with the limbic network. We also predicted that the distinct functional connectivity alterations would be associated with the contamination/washing symptom severity.

2. Methods

2.1. Participants

The study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System. We recruited 27 OCD patients from the psychiatric outpatient clinic of Severance Hospital, Yonsei University College of Medicine. Diagnosis of OCD and screening of healthy controls (HC) were performed using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). For OCD participants, any cases with current diagnoses of Axis I disorders other than OCD, minor depression, and social phobia were excluded. The Yale–Brown Obsessive–Compulsive Scale and Symptom Checklist (Y-BOCS) (Goodman et al., 1989) was used to assess OC symptom severity and dimensions. Each of the major categories of the Y-BOCS symptom checklist was assigned a score of 0 (absent symptom), 1 (symptom present but not a major reason for concern), or 2 (prominent symptom). The major symptom dimension scores were then computed using the algorithm described by Mataix-Cols et al. (1999). Briefly, the "contamination/washing" score was the sum of "contamination obsessions" and "washing/cleaning compulsions" divided by 2; the "harm/checking" score was the sum of "aggressive obsessions" and "checking compulsions" divided by 2; and the "symmetry/ordering" score was the sum of "symmetry obsessions," "ordering compulsions," "repeating compulsions," and "counting compulsions" divided by 4. The practice of dividing by the number of items in each dimension ensured comparable score ranges across dimensions. Because only two patients in our sample exhibited hoarding or sexual/religious symptoms ≥2, these dimensions were not analyzed in this study. We considered patients to be in the contamination/washing (CON) group if contamination obsessions or cleaning compulsions were currently present and were major problems for the patient, with a score of at least 2 for at least one of these symptoms. Patients without contamination/washing symptoms (NCON group) did not exhibit any current contamination obsessions, cleaning compulsions, or any past principal symptom under this category. With regard to psychiatric comorbidity, one subject each from the CON group and NCON group presented with social anxiety disorder. Three subjects in the CON group and 2 in the NCON group had depressive disorder not otherwise classified as comorbidity. All OCD participants were taking a stable dose of medication for at least 3 months before the MRI scan, except for one patient in the CON group who was medication-free for more than a month before the scan (Table 1).

We recruited 19 age- and gender-matched HC via postings in the hospital and local newspaper advertisements. Any participants with a past or current diagnosis for any Axis I disorder, past or current drug abuse/dependence (except nicotine and caffeine), or neurological disorders were excluded. Depression and anxiety severities were measured using the Beck Depression Inventory (Beck et al., 1961) and the Beck Anxiety Inventory (Beck and Steer, 1990), respectively. In addition, all participants completed the Disgust Scale—Revised to measure disgust sensitivity (Olatunji et al., 2007). We also excluded any participants with contraindications for a general functional magnetic resonance imaging (fMRI) experiment. One of the patients withdrew from the experiment before fMRI scanning, and data from one HC was excluded from analysis due to noise from movements. Thus, a total of 13 patients in the CON group, 13 patients in the NCON group, and 18 in the HC group were included in the final analysis. After complete description of the study to the subjects, written informed consent was obtained. All the process of this study was carried out in accordance with the latest version of the Declaration of Helsinki.

Table 1
Demographics and clinical characteristics of participants.

	CON group ($N = 13$)		NCON group ($N = 13$)		HC group ($N = 18$)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	28.2	7.4	26.3	4.8	28.2	6.6
Education (years)[a]	15.2	1.8	14.6	2.2	16.6	1.1
Onset age (years)	16.9	6.2	14.7	4.0		
Duration of illness (years)	10.9	7.6	11.8	6.5		
Y-BOCS total	20.1	6.9	24.2	5.1		
Y-BOCS contamination/washing[b]	3.6	0.7	0.9	1.0		
BDI[c]	17.4	11.3	16.7	10.6	3.4	3.0
BAI[c]	22.7	9.7	21.1	15.9	4.8	5.4
Disgust scale total[c]	54.7	9.3	59.1	11.1	45.2	8.4
	N	%	*N*	%		
Medication at study time						
Medication-free (>1 month)	1	7.7	0	0		
SSRI	6	46.2	7	53.8		
SSRI combinations	2	15.4	2	15.4		
Antipsychotic augmentations	4	30.8	4	30.8		

CON, contamination; NCON, non-contamination; HC, healthy control; SD, standard deviation; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SSRI, selective serotonin reuptake inhibitor.
[a] Indicates significant difference between NCON group and HC group ($P < 0.05$).
[b] Indicates significant difference between CON and NCON group ($P < 0.001$).
[c] Indicates significant difference between OCD patients and HC group ($P < 0.001$).